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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,471	03/15/2004	Joseph P. Lyssikatos	PC11078C	1808

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EXAMINER	
BALLS, ROBERT J	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 08/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/801,471	LYSSIKATOS ET AL.	
	Examiner	Art Unit	
	R. James Balls	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-35* is/are pending in the application.

4a) Of the above claim(s) *29-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 29-35 are pending.

2. This application is a divisional application of U.S. Patent Application Serial No. 10/441,567, filed on May 20, 2003, now U.S. Patent No. 6,734,308, which is a divisional of U.S. Patent Application Serial No. 10/021,201, filed on December 7, 2001, now U.S. Patent No.6,645,982, which claims benefit of U.S. Provisional Application No. 60/256,598, filed on December 19, 2000.

3. Claims 33-35 are under examination. Claims 29-32 are withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 33-35 are rejected under 35 U.S.C. §103(a) as being unpatentable over WO0012499 (La Greca & Lyssikatos) in view of Berge et al., *Pharmaceutical Salts*, J. PHARM. SCI. 66(1):1-19 (1977).

Determination of the scope and content of the prior art (MPEP §2141.01)

The prior art discloses methods of treating hyperproliferative disorders with pharmaceutically acceptable salts of 6-[(4-chloro-phenyl)-hydroxy-(3-methyl-

3H-imidazol-4-yl)-methyl]-4(3-ethynyl-phenyl)-1methyl-1h-quinolin-2-one, 2,3,-dihydroxybutanedioate. See the abstract and Example 3 on page 27. Also, the prior art's specification lists tartrate as an acceptable pharmaceutical salt on page 8, line 32. Berge et al., explain that tartrate is a salt approved by the FDA for pharmaceutical use. See page Table 1 on page 2. Note also that not all salts are approved for use in pharmaceuticals. See page Table on page 3.

WO0012499 (La Greca & Lyssikatos) also teaches methods of treating hyperproliferative disorders with *6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4(3-ethynyl-phenyl)-1methyl-1h-quinolin-2-one, 2,3,-dihydroxybutanedioate* and an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens. See the paragraph beginning on page 5, line 30.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The claims differ from the prior art in that the claims specifically require the corresponding pharmaceutically acceptable salt to be tartrate, whereas the prior art provides for an array of pharmaceutically acceptable salt, including tartrate.

Finding of prima facie obviousness-rationale and motivation (MPEP §2142-2143)

One of ordinary skill in the art would be motivated to use tartrate as a pharmaceutically acceptable salt with a reasonable expectation of success for

two reasons: (1) because the reference specifically teaches that tartrate is a useable salt of 6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4(3-ethynyl-phenyl)-1methyl-1h-quinolin-2-one, 2,3,-dihydroxybutanedioate in the treatment of hyperproliferative disorders, and (2) because FDA has approved tartrate for use in pharmaceuticals. The skilled artisan in field of pharmaceutics would be motivated to employ a salt approved for use in the treatment of human disease. Berge et al. provides lists of both approved and non-approved salts on pages 2-3, Tables I and II.

The instant claims also require that the salt be in crystal form. Using a new crystal structure of a compound (polymorph) to treat disease does not provide any different merit to the known method of treating a disease because the crystal dissolves inside the body and loses its novel characteristics, i.e. its unique lattice structure. Harry G. Brittain, POLYMORPHISM IN PHARMACEUTICAL SOLIDS 1-2 (Marcel Dekker, Inc. 1999), explains, "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules." See page 2. The different arrangements and/or different conformations of the molecules disappear and become irrelevant upon dissolution of the crystal in the body's aqueous environment. Rowland & Tozer, CLINICAL PHARMACOKINETICS (Williams and Wilkins 1995) illustrate the process by which pharmaceutical compositions travel through the body. See page 123. This graphic shows that the drug travels into the stomach, through the gut wall, into the portal vein to the liver. The drug that withstands the liver travels through

the blood to a target site where it exhibits its therapeutic function. At the target site, because the drug molecules bind to a receptor or enzyme one at a time, the crystal must be dissolved in order to bind. Silverman, THE ORGANIC CHEMISTRY OF DRUG DESIGN AND DRUG ACTION, (Academic Press, Inc.) pictorially illustrates molecular action of protein/substrate binding. See page 73. One of ordinary skill in the art would expect the tartrate salt of the instant compound to function by an identical mechanism as the prior art upon dissolution inside the body, therefore rending the instant claims obvious.

5. Claims 33-35 are rejected under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 6,150,377 (Lyssikatos & La Greca) in view of Berge et al., *Pharmaceutical Salts*, J. PHARM. SCI. 66(1):1-19 (1977) for the same reasons provided in Section 4 above, which is incorporated herein.

The applied reference has a common assignee and one common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. §102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and

reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Double Patenting

6. Claims 33-34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-13 of U.S. Patent No. 6,150,377 in view of Berge et al., *Pharmaceutical Salts*, J. PHARM. SCI. 66(1):1-19 (1977). Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons given above in section 4, which is incorporated herein.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an

invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim Rejections - 35 USC § 112 (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact t+erms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The rejection of Claims 33-35 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement is maintained. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to use the invention commensurate in scope with the breadth of the claims. The claims are drawn to a method of treating all hyperproliferative disorders. Cancer treatment, however, is drug and cancer specific, that is, a particular compound may treat a particular cancer, but no general extrapolation can be warranted in absence of a multiple cell line testing. See Grever et al., *The National Cancer Institute: Cancer Drug Discovery and Development Program*, SEMINARS IN ONCOLOGY, 19:6 622-638 (1992). Grever et al. explains that the ability of a compound to treat one type of cancer cell line is not predicative of the compounds ability to treat other types of cancers cell lines. Therefore, the NCI has implemented screening protocols that quantify a compound's anti-cancer potential over a panel of sixty human tumor cell lines,

derived from seven cancer types (lung, colon, melanoma, renal, ovarian, brain, and leukemia). See the end of page 626.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Courts rely on the following factors set out in *In re Wands* to determine whether undue experimentation is required to practice a claimed invention, i.e. whether the claimed invention is enabled:

(a) The breadth of the claims;
(b) The nature of the invention and predictability in the art;
(c) The state of the prior art;
(d) The level of one of ordinary skill;
(e) The existence of working examples; and
(f) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407.

The analysis is applied to the instant case.

(a) The claims are drawn to a method of treating all hyperproliferative disorders. The specification does not provide a precise definition for term "hyperproliferative disorder," but says that hyperproliferative diseases include

cancer. See last sentence on page 1 of the specification. Therefore, the claim includes all types of hyperproliferative disorders including benign tumors and all types of cancers.

(b) The invention is physiological in nature as it is directed toward pharmaceuticals and treating diseases with those pharmaceuticals, an art which is highly unpredictable. "[T]he scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). In the highly unpredictable pharmaceutical art, the required disclosure is greater than for the disclosure of an invention involving predictable factors such as mechanical or electrical elements. *In re Vaeck*, 20 USPQ 2d 1438 (CAFC 1991). Cancer treatment, in particular, is an unpredictable art and no known compounds are available capable of treating all types of cancer.

(c) The state the art is such that cancer treatment is drug and cancer specific, that is, a particular compound may treat a particular cancer, but no general extrapolation can be warranted in absence of a multiple cell line testing. See supra.

(d) The level of skill required to practice the invention is high due to its pharmaceutical nature.

(e) The specification contains no working examples demonstrating the compounds ability to treat any particular cancer. The specification on page 13, line 15 shows that a limited number of compounds have Ras farnesylation

inhibition activity. However, such activity has not been inextricably linked to any particular cancer, just generally to nearly all cancers.

(f) The quantity of experimentation necessary to use the disclosed invention is high. Because no indication as to what types of cancers can be treated with the disclosed compounds, the skilled artisan is subject to undue experimentation to determine which type of hyperproliferative disorders can actually be treated.

Based on the limited disclosure, the unpredictability in the art, and the level of skill required to practice the invention, the skilled artisan would be subject to undue experimentation to determine how to use the invention commensurate in scope with the breadth of the instant claims.

Claim Rejections - 35 USC § 112 (Written Description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 35 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The invention must be described, "with such clarity that the reader is assured that the inventor actually has possession and knowledge of the unique composition that makes it

worthy of patent protection." *University of Rochester v. G.D. Searle & Co., Inc.*, 249 F. Supp. 2d 216 (W.D. N.Y. 2003) *affirmed* 358 F.3d 916 (Fed. Cir. 2004). An adequate written description thus "guards against the inventor's overreaching by later claiming that which he did not invent, by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas-Cath v. Mahurkar*, 935 F.2d at 1561 (Fed.Cir. 1991).

The claim is drawn to a method of treating a hyperproliferative disorder with *6-[(4-chloro-phenyl)-hydroxy-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-ethynyl-phenyl)-1-methyl-1H-quinolin-2-one, 2,3-dihydroxy butanedioate anhydrous salt* in combination with and an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens. Definitions for each group of anti-tumor agents does not exist and representative species are not shown. Therefore, the claim reaches through to future compounds not yet known or discovered. This broad protection would give applicants patent protection extending beyond that which is described in the specification, known in the art, or possessed by applicants in violation of 35 U.S.C. §112.

For a more detailed explanation and commentary on reach-through claims, see LeCointe, *Reach-Through Claims*, INTERNATIONAL PHARMACEUTICAL (2002) (also available at:

http://www.bakerbotts.com/infocenter/publications/detail.aspx?id=bffe4a7d-5beb-4cf8-a189-15a5f190f0eb) and Silva, *Reach Through Claims: Bust or Boon?*, INTELLECTUAL PROPERTY UPDATE (available at: http://www.dorsey.com/publications/legal_detail.aspx?FlashNavID=pubs_legal&pubid=170565003)

These articles draw their conclusions from *Rochester v. G.D. Searle & Co.*, 358 F.3d 916 (Fed. Cir. 2004). As the articles point out, claims such as "a method of treating a disease by administering a compound which is an enzyme X agonist," where there is no additional description of such a compound (i.e. chemical formula) is considered a reach-through claim. Applicants' claim is similar in that it is drawn to a anti-tumor agents such as alkylating agents, where there is no additional description of such agents.

Claim Rejections - 35 USC § 112 (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

9. Claim 35 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the claimed invention. The claim reaches into future anti-tumor agents. The

skilled artisan cannot practice a method of treating a hyperproliferative disorder with a compound that has not been discovered.

Conclusion

10. No Claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to R. James Balls whose telephone number is (571) 272-7997. The examiner can normally be reached on Mon - Fri 8:00am - 4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tom McKenzie can be reached on (571) 272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

R. James Balls
August 2, 2006

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